NDA 50-091/S-008

Allergan
Attention: Elizabeth Bancroft
Senior Director, Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

OCT 3 2000

Dear Ms. Bancroft:

Please refer to your supplemental new drug application dated August 5, 1981, received August 10, 1981, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Chloroptic (chloramphenicol ophthalmic solution, USP) 0.5%. We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated July 23, 1991, and September 15, 2000. Your submission of July 23, 1991 constituted a complete response to our April 1, 1991 action letter.

This supplemental new drug application provides for revised labeling of the package insert.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling of the package insert submitted September 15, 2000.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be desiguated “FPL for approved supplement NDA 50-091/S-008.” Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090. Sincerely,

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

DRAFT LABEL

Chloroptic® (chloramphenicol ophthalmic solution, USP) 0.5% sterile

WARNING
Bone marrow hypoplasia including aplastic anemia and death has been reported following topical application of chloramphenicol. Chloramphenicol should not be used when less potentially dangerous agents would be expected to provide effective treatment.

DESCRIPTION

Chloroptic® (chloramphenicol ophthalmic solution, USP) is a topical *anti-infective* product for ophthalmic use.

Structural Formula

(Structure)

chloramphenicol

$C_{11}H_{12}Cl_{12}N_20_5$

Mol Wt 323.13

Chemical Name:
D-threo-(-)-2,2-Dichloro-N-143-hydroxy-a-(hydroxymethyl)..
p-nitrophenethyl] acetamide

Contains:

Active: chloramphenicol	0.5% (5mg/ml)
Preservative: chlorobutanol (chloral deny.)	0.5%;

Inactives: polyethylene glycol 300; polyoxyl 40 stearate; sodium hydroxide or hydrochloric acid to adjust PH; and purified water.

CLINICAL PHARMACOLOGY

Microbiology

Chloramphenicol is a broad-spectrum antibiotic originally isolated from *Streptomyces venezuelae.* It is primarily bacteriostatic and acts by inhibition of protein synthesis by interfering with the transfer of activated amino acids from soluble RNA to ribosomes.

Chloramphenicol has been shown to be active against the following organisms:
Aerobic gram-positive microorganisms:

Staphylococcus aureus
streptococci, including *Streptococcus pneumoniae*
Aerobic gram-negative microorganisms:
Enterobacter sp.
Escherichia coli
Haemophilus influenzae
Klebsiella sp.
Moraxella lucunata (Morax-Axenfeld bacillus)
Nesseria sp.

This product does not provide adequate coverage against *Pseudomonas aeruginosa or Serratia marcescens.*

Bacteriological studies should be performed to determine the causative organisms and their susceptibilities to chloramphenicol.

INDICATIONS AND USAGE
Chioramphenicol should be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. (See Boxed Warning)

Chloroptic is indicated for the treatment of surface ocular infections involving the conjunctiva and/or cornea caused by chloramphenicol-susceptible organisms. Chloramphenicol is active against the following common bacterial eye pathogens: *Staphylococcus aureus;* streptococci, including *Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzea, Klebsiella/Enterobacter* species; *Moraxella lacunata* (Morax-Axenfeld bacillus); and *Neisseria species.* Chloramphenicol does not provide adequate coverage against: *Pseudomonas aeruginosa* or *Serratia marcescens.*

CONTRAINDICATIONS
This product is contraindicated in persons sensitive to any of its components.

WARNINGS
SEE BOXED WARNING
Occasionally one sees hematopoietic toxicity with the use of systemic chloramphenicol, and rarely with topical administration. This type of blood dyscrasia is generally a dose-related toxic effect on bone marrow and is usually reversible on cessation of the drug. Rare cases of aplastic anemia have been reported with prolonged (months to years) or frequent intermittent (over months and years) use of topical chloramphenicol.

PRECAUTIONS
General: The prolonged use of antibiotics may occasionally result in overgrowth of nonsusceptible organisms, including fungi. If new infections appear during medication or clinical improvement is not observed within 1 week, the drug should be discontinued and appropriate measures should be taken.

Information for patients: Do not touch bottle tip to any surface as this may contaminate the

solution.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No long-term studies have been conducted in animals or in humans to evaluate the carcinogenic potential or effects on fertility with chloramphenicol. However, there is some clinical evidence that aplastic anemia due to chloramphenicol may be associated with subsequent development of leukemia.

Pregnancy
Pregnancy Category C. Chloramphenicol has been shown to be embryocidal and teratogenic in rat, mouse, rabbit and chicken embryos/fetuses (see below). There are no adequate and well-controlled studies in pregnant women. Chloramphenicol has been shown to cross the placental barrier, but it is not known whether chloramphenicol can cause fetal harm when administered to a pregnant woman. Chloramphenicol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Embryotoxic effects: Significantly lower numbers of live fetuses and an increase in the number of early embryonic resorptions occurred after pregnant rats were treated orally with 500 mg/kg (equivalent to 5800 times the recommended maximum daily adult topical ophthalmic dose) from days 5 to 15 of their pregnancy. Similar findings were seen with groups receiving higher oral doses (1000 mg/kg or 2000 mg/kg) at various dosing intervals. Female mice receiving 1000 mg/kg orally from days 6 to 12 of their pregnancy showed a significant increase in the number of resorptions. Female rabbits receiving the same oral dosing (1000 mg/kg) from days 8 to 11 had an increase in the number of resorptions of embryos without placentation. Chioramphenicol (2.5 mg) injected into chicken eggs resulted in a 20% embryo mortality rate one day after administration, which increased to 100% embryo mortality on the 11th day of incubation.

Teratogenicity: When given to female orally at 2000 mg/kg from days 6 to 8 of pregnancy, 36% of the fetuses exhibited either an omphalocele or an umbilical hernia, with costal fusions. Fetuses of the rats treated with 1000 mg/kg orally from days 7 to 12 of pregnancy or 2000 mg/kg from days 11 to 13, and of mice treated with 1000 mg/kg from days 6 to 12, had a higher incidence of missing ossification of the phalangeal nuclei of the forelegs and hindlegs; and of the 5th stemebra. This correlated with a decrease in the average weight of the fetuses. Rabbit fetuses displayed more frequent absence of the phalangeal nuclei of the forelegs than control when pregnant rabbits received 500 mg/kg orally on days 6 to 15 of pregnancy, More frequent missing ossification of the phalangeal nuclei of the forelegs and hindlegs and an increase in the number of unevenly ossified vertebrae was seen in the fetuses of rabbits when pregnant females were given 1000 mg/kg from days 6 to 9 of pregnancy.

Teratogenic effects of chioramphenicol (0.5 mg when injected into chicken eggs, included malformations of the beak, eyes and legs.

Nursing Mothers: Chloramphenicol appears in human milk following oral administration of the drug. Systemic absorption of chloramphenicol may occur when applied topically. Because of the potential for serious, adverse reactions in nursing infants from chioramphenicol, a

decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy in pediatric patients below 1 year of age have not been established.

Geriatric Use: No overall difference in safety or effectiveness have been observed between elderly and younger, adult patients.

ADVERSE REACTIONS

Exact incidence figures are not available since no denominator of treated patients is available.

The most serious reaction following prolonged or frequent intermittent use of topical chloramphenicol is bone marrow aplasia.

The most frequently reported adverse reactions have been burning, stinging, ocular irritation, and conjunctival hyperemia. Blood dyscrasias, allergic or inflammatory reactions due to individual hypersensitivity, angioneurotic edema, urticaria, vesicular and maculopapular dermatitis have also been reported (See Warnings and Box Warning).

DOSAGE AND ADMINISTRATION

One or two drops 4 to 6 times a day for the first 72 hours should be placed in the lower conjunctival sac. Treatment should be continued for approximately 7 days but should not be continued for more than three weeks without re-evaluation by the prescribing physician.

HOW SUPPLIED

Chloroptic (chloramphenicol ophthalmic solution, USP) is supplied in the following sizes:

2.5 mL . NDC 11980-109-03
7.5 mL . NDC 11980-109-08

NOTE: Refrigerate until dispensed. Then store below 30°C (86F). Discard solution within 21 days from date dispensed.

Rx only.
U.S. Patent 3,702,364
Revised July 2000

Irvine, CA 92612